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Surveillance for meningococcal disease and strategies for use of conjugate meningococcal vaccines in the United States

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Abstract

Background: *Neisseria meningitidis* is a leading cause of bacterial meningitis in US; new capsular type-specific conjugate vaccines offer an opportunity for improved control of meningococcal disease. We evaluated the relative burdens of invasive meningococcal disease in US and examined the projected impact of various meningococcal conjugate vaccination strategies on rates of meningococcal disease. *Methods:* meningococcal disease incidence rates were determined from active, population-based surveillance in selected US areas. Models were created to determine impact of vaccination of infants, toddlers, adolescents or college students with meningococcal conjugate vaccines, with assumptions for vaccine coverage, efficacy and duration of protection. Although we examined possible conjugate vaccine formulations including serogroups A, C, Y and W-135, the final vaccine impact analysis excluded serogroups A and W-135. Outcome measures were cumulative meningococcal disease incidence, and incidence 10 years after initiating vaccination among 0–22-year-olds. *Results:* in models of serogroup C + Y meningococcal conjugate vaccination of infants, toddlers and adolescents, the cumulative incidence of meningococcal disease was reduced by 54, 48 and 25%, respectively; the toddler strategy had the greatest impact per dose. After 10 years of routine meningococcal conjugate vaccination, meningococcal disease could be reduced by 50% and deaths by 64%. *Conclusions:* use of meningococcal conjugate vaccine could markedly reduce meningococcal disease incidence. Our data, along with vaccine formulation and vaccination program considerations, will be important in determining the optimal choice of vaccination strategy. Published by Elsevier Science Ltd.

Keywords: Neisseria meningitidis; Meningococal; Conjugate vaccine

1. Background

A decade ago, most bacterial meningitis was caused by three encapsulated organisms, *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis* [1,2]. Introduction of Hib conjugate polysaccharide vaccines in the late 1980s resulted in a 99% decrease in Hib disease [3]; one of the most notable US public health achievements of the last decade. Pneumococcal conjugate vaccines against the most common *S. pneumoniae* serotypes causing invasive disease in the US have recently become available for integration into routine childhood immunization [4]. Similarly, meningococcal conjugate vaccines are also in development and may offer an opportunity to dramatically reduce the incidence of meningococcal disease.

In US, approximately 2400 cases of meningococcal disease occur per year [5], however, this relatively low disease incidence fails to convey the full impact of disease. Meningococcal disease can rapidly progress and cause high morbidity and mortality despite early use of appropriate antibiotic therapy. Furthermore, each case requires a public health response involving labor-intensive contact tracing and antimicrobial chemoprophylaxis. Outbreaks of meningococcal disease require costly emergency vaccination campaigns [6,7]. For all these reasons, prevention of meningococcal disease is a public health priority.

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The only meningococcal vaccine licensed and available in US is a quadrivalent polysaccharide vaccine that protects against serogroups A, C, Y, and W-135. Since it has a short duration of protection [8,9] and is poorly immunogenic in infants <2 years [10,11], who are at greatest risk of disease, meningococcal polysaccharide vaccine is not recommended for routine childhood immunization [6]. Serogroup B strains, which cause about one-third of disease in US, have a capsular polysaccharide that is poorly immunogenic in all humans, so development of a serogroup B vaccine is progressing along alternative pathways [12,13]. Serogroup B vaccines for routine use are unlikely to be available in US for at least 5–10 years.

Several meningococcal conjugate vaccine formulations are undergoing clinical trials in US and should soon be available for use [14]; these vaccines should improve immune response to meningococcal serogroups A, C, Y and W-135 polysaccharide antigens in infants and young children [15] and provide longer duration of protection for all ages [16]. In UK, with a high burden of endemic meningococcal disease, such expectations led to initiation of routine childhood immunization with a serogroup C meningococcal conjugate vaccine in November 1999 [17]. Routine use of similar vaccines in US may offer the first major opportunity for control of endemic meningococcal disease in this country.

However, multiple strategies for implementing routine use of these vaccines are possible. Since meningococcal disease affects a broad age-range, intervention at a variety of points in the vaccination schedule should be considered, including infants, toddlers, adolescents and young adults at college entry. In addition, changes in the distribution of meningococcal serogroups over time complicate the choice of vaccine formulation. Finally, combination vaccines including meningococcal serogroups combined with pneumococcal conjugate, Hib, diphtheria-pertussis-tetanus or other existing vaccines are technically possible and could reduce the number of recommended childhood injections.

We used active, population-based surveillance data to examine US burden of meningococcal disease and incorporate this into quantitative models to assess the impact of several strategies for use of meningococcal conjugate vaccines to help advocate for strategies that will maximize public health impact.

2. Methods

2.1. Surveillance data

Surveillance for invasive disease caused by *N. meningitidis* is conducted as a part of the Active Bacterial Core Surveillance (ABCs) [1,18]. This ongoing, population-based active surveillance is a part of the Emerging Infections Program Network coordinated by the Centers for Disease Control and Prevention (CDC) in collaboration with participating state and local health departments and universities. We used ABCs data collected from January 1, 1990, through 31 December 1998. The participating surveillance sites during this time were the states of Connecticut, Georgia, Maryland, Minnesota, Missouri, and Oklahoma along with the five most populous counties in Tennessee, the San Francisco Bay Area, and the Rochester, New York, metropolitan area. Initiation and duration of surveillance varied by site, with the total population under surveillance varying by year from 10 million persons in 1990 to 30 million in 1998.

For this study, we defined a case of meningococcal disease as isolation of *N. meningitidis*, from a clinical specimen taken from a normally sterile site in a surveillance area resident. Meningococcal meningitis were defined as isolation of *N. meningitidis*, from cerebrospinal fluid or isolation from blood with associated clinical meningitis. Demographic, clinical and laboratory data were collected for each case. Serogroup identification was performed at CDC or in the respective state for all isolates; we used CDC serogroup results, when CDC and state results were discrepant.

To assess the sensitivity of reporting and case ascertainment, hospitals were periodically audited by review of microbiology records. Based on these audits, surveillance personnel detected 96–98% of meningococcal cases prior to audit; additional cases identified by audit were included in the analysis.

2.2. Calculation of standardized incidence rates

Rates of disease among the surveillance populations were calculated using US Bureau of the Census post-census population estimates [19]. National projections of cases were estimated by applying race- and age-specific rates of disease for the aggregate surveillance areas to the racial and age distribution of the US population. Race was defined as black, white or other. Race specification was missing in 7% of cases; missing designations were distributed into specific race categories based on the reported race distribution for cases with known race within each age category. Similarly, in 15% of cases, the serogroup was unknown; these were distributed into specific serogroup categories within each age-race group based on the distribution of cases with known serogroup in the same age-race group. Within each age-group, serogroup-specific rates and projected cases were estimated by applying the proportion of each serogroup within the age-group to the age-group specific rate and projected cases.

2.3. Calculation of cumulative incidence rates

To calculate cumulative incidence rates, we assumed that age-group-specific incidence rates were constant for each single year within the age-group. Since immunologic memory induced by other protein antigen vaccines has been demonstrated to elicit protection for nearly 2 decades [20,21] and conjugate meningococcal vaccines have been demonstrated to also induce immunologic memory [22], a long duration of protection is expected from a meningococcal conjugate vaccination strategy. Since most meningococcal disease occurs in the first 2 decades of life, and to simplify the calculations of vaccine impact through all age-groups examined, we chose a duration of protection of 22 years. Serogroup-specific cumulative incidence rates through the first 22 years of life were calculated by summing the age-specific projected cases for each single year of age divided by the population of 0–22-year-olds. Incidence rates were calculated for the following age groups: infants (0–23 months), toddlers (2–4 years), adolescents (11–17 years) and college students (18–22 years).

2.4. Calculation of vaccine impact

We modeled four vaccination strategies separately and in combination (Table 1). The strategies were based, in part, on recommendations for Hib and pneumococcal conjugate vaccination [23,24]. Although an infant or toddler 15–18 month booster dose may be required, our analysis included only the primary vaccination series. As with the cumulative incidence rate, we assumed a steady-state US population with constant age-specific rates over time and a duration of protection by the vaccine of at least 22 years.

Cumulative impact was calculated (Table 2) by following the 1998 US annual birth cohort (persons <1 year of age) [19] over the first 22 years of life after vaccination as described for each strategy. Impact was calculated as total disease or deaths during the cumulative time period, and disease and deaths averted per million doses of vaccine administered in the primary series (three doses for the infant and one dose for the toddler strategy).

We evaluated the sensitivity of our model to variations in age-specific vaccination coverage and vaccine efficacy by calculating vaccine impact projections for two vaccination coverage scenarios. The 'ideal' scenario assumed 100% vaccination coverage for all targeted age-groups and, for persons ≥ 1 year of age, a serogroup-specific vaccine efficacy of 97% after a single dose of vaccine, based on estimates of efficacy during infancy after four doses of pneumococcal conjugate polysaccharide vaccine [4]. To account for the developing infant immune response, for infants <1 year of age, we assumed an efficacy of 0% before and 97% after the second dose of vaccine at 4 months of age. A 'current' scenario assumed 1998 US age-specific coverage levels. Vaccination coverage rates for the age-groups 5–11 months and 1 year were taken from National Immunization Survey data for Hib immunization among children at 7, 13, and 24 months of age [25]. Coverage in the 2–4-year age-groups was taken from national data for three doses of Hib [26], and coverage of 5–10-year-olds was taken from national school entry immunization data [27]. Due to the sparse data on vaccination coverage rates for the adolescent (11–17-year-old) age group, we used a rate of 66% based on hepatitis B virus vaccination coverage among 11-year-olds in Florida of 62% in 1997 [28] and 71% in North Carolina in 1996 [28,29]. The 'current' scenario also assumed a lower vaccine efficacy estimate of 93% based on efficacy of two doses of Hib vaccine in infants [30,31]. To evaluate a college-based vaccination schedule, we assumed 100% coverage of the 36% of persons

Table 1
Meningococcal conjugate vaccination strategies and vaccine coverage assumptions

Vaccination strategy	Doses given for primary vaccination series[a]	Age-group-specific vaccine coverage (%)[b] under ideal/current assumptions[c]						
		0–4 months[c]	5–11 months	12–23 months	2–4 years	5–10 years	11–17 years	18–22 years
Infant	2, 4, and 6 months	100/63	100/63	100/87	100/93	100/98	100/66	100/100
Toddler	12 months	0/0	0/0	100/87	100/93	100/98	100/66	100/100
Adolescent	11 years	0/0	0/0	0/0	0/0	0/0	100/66	100/100
College	College entry (18 years)	0/0	0/0	0/0	0/0	0/0	0/0	100/100

[a] Although an infant or toddler 15–18 month booster dose may be required, this analysis models only the primary vaccination series.
[b] Catch-up coverage assumed to occur for each strategy [24–28].
[c] Efficacy chosen to be 97% under ideal assumptions and 93% under current assumptions after a single dose of conjugate vaccine for ages ≥ 1 year and after two doses for ages 4–11 months; efficacy was assumed to be 0% from birth to age 4 months for all strategies [4,29,30].

Table 2
Formulae used for modeling

Calculation	Formula
Cumulative incidence (0–22 years)	
Baseline	$\Sigma_{i=1}^{7}\Sigma_{j=1}^{6} Y_i R_{ij}$
Infant, toddler or adolescent schedule[a]	$\Sigma_{i=1}^{7}\Sigma_{j=1}^{6} Y_i(1-C_iE_i)R_{ij}$
Vaccine impact (meningococcal disease cases) during 10th year after initiating vaccination strategy[b,c]	
Infant, toddler or adolescent schedule	$\Sigma_{i=1}^{7}\Sigma_{j=1}^{6} [Y_i(1-C_iE_i)R_{ij}P_i]/10\times 5$
Definitions[d]	R_{ij} = Baseline meningococcal disease/death rate for age-group i, serogroup j Y_i = Number or fraction of years in age group i C_i = Vaccination coverage for age group i E_i = Vaccination efficacy for age group i P_i = 1998 US population for age group i

[a] Fixed population cohort progressing from birth through age 22 years; 22 years protection and constant age-specific incidence rates assumed.

[b] Calculation is for incidence due to serogroups present in proposed vaccine formulations. Disease/death due to serogroups not represented in proposed vaccine formulation included by adding in baseline rates of disease/deaths due to those serogroups.

[c] After 10 years of infant or adolescent strategy vaccination, all persons 0–9 or 11–19 years of age, respectively, would have been eligible for vaccination. Age groups were divided accordingly to determine populations covered by vaccination.

[d] Age-groups: i = 1:0–4 months; i = 2:5–11 months; i = 3:12–23 months; i = 4:2–4 years; i = 5:5–10 years; i = 6:11–17 years; i = 7:18–22 years; i = 8:23–64 years; i = 9: ≥65 years; serogroups-j = 1–6 corresponding to serogroups A, B, C, Y, W-135 and other, respectively; incidence rates (R_{ij}) based on age-group and race-specific surveillance data projected to US population at the time of surveillance.

18–22 years of age enrolled in undergraduate institutions [32].

In addition to looking at impact of vaccination assuming ideal and current values for coverage and efficacy, we evaluated the sensitivity of our model to changes in efficacy and coverage by calculating the reduction in cumulative disease or deaths through use of a C + Y meningococcal conjugate vaccine in each vaccination strategy for various combinations of efficacy (60, 80 or 100%) and coverage (40–100%, in 10% increments) applied simultaneously to all age groups.

We calculated the impact of specific vaccination strategies using age-group-specific, race-adjusted, nationally projected rates to determine cases of meningococcal disease and deaths that could be expected during the tenth year after initiating vaccination with either a monovalent serogroup C or a bivalent C + Y meningococcal conjugate vaccine formulation.

2.5. Statistical analysis

Incidence rates and vaccination impact were calculated using SAS™ for Windows statistical analysis software (version 6.12, The SAS Institute, Cary, NC) and Excel for Windows (version 7.0, Microsoft Corporation, Redmond, WA).

3. Results

From 1990 to 1998, we detected 1886 cases of meningococcal disease, for an annual incidence in the surveillance areas of 1.1 cases/100,000 population. The overall race-adjusted, US projected rate of meningococcal disease was also 1.1 cases/100,000 population. Rates were highest for serogroup B during infancy, with serogroups C and Y predominating in toddlers and adolescents (Fig. 1). The proportion of disease caused by specific serogroups changed during the decade with, most notably, serogroup Y disease increasing from 2% in 1990–1992 to 37% in 1996–1998. Overall from 1990 to 1998, the proportions of total disease attributed to serogroups B, C and Y were 27, 36, and 29%, respectively. Mortality from meningococcal disease was 10% for all ages combined, 8% during the first 22 years of life, and 13%, for persons10–22 years of age. Among persons 0–22 years of age, 59% of meningococcal disease presented as meningitis, compared with 49% for all ages.

Through the cumulative incidence analysis, we examined the potential impact of specific vaccine formulations and vaccination strategies on rates of meningococcal disease and deaths among persons 0–22 years of age (Table 3A). We assessed the potential impact of including various serogroup components in a conjugate vaccine formulation. However, since serogroups C and Y are the principal causes of disease for which a conjugate polysaccharide vaccine is available, the results reported here focus on formulations with one or both of these serogroups. By calculating age-group specific incidence rates from the full 9-year surveillance data, the effect of transient variations in age-group specific incidence rates on impact of vaccination strategies are minimized (data not shown). Compared with the serogroup C conjugate vaccine, the serogroup C + Y conjugate vaccine could prevent 280 (48%), 235 (44%) and 150 (60%), more cases of meningococcal disease in the infant, toddler or adolescent strategy, respectively. Although rates of meningococcal disease are highest during infancy, the toddler strategy would leave infants unprotected for only 7 months more than the infant strategy; an infant strategy using the C + Y formulation would prevent 88 more cases and three more deaths than a toddler strategy. However, since three doses are needed for the

Table 3
Impact of vaccination strategies: cumulative analysis

Vaccination strategy	Serogroup C vaccine				Serogroup C+Y vaccine			
	Disease remaining	(%) reduction	Deaths remaining	(%) reduction	Disease remaining	(%) reduction	Deaths remaining	(%) reduction
A *Cumulative meningococcal disease/deaths over first 22 years of life and percent decrease from unvaccinated baseline after specific vaccination strategy using serogroup C or C+Y meningococcal conjugate vaccine*								
No vaccination baseline	1605	–	127	–	1605	–	127	–
Infant	1026	36	59	54	746	54	39	69
Toddler	1069	33	62	51	834	48	42	67
Adolescent	1359	15	91	28	1209	25	73	42

B *Cumulative meningococcal disease/deaths averted per dose of vaccine*[b] *over first 22 years of life*[a] *after specific vaccination strategy using serogroup C or C+Y meningococcal conjugate vaccine*				
	Disease averted/10^6 doses	Deaths averted/10^6 doses	Disease averted/10^6 doses	Deaths averted/10^6 doses
Infant	51	6	76	8
Toddler	142	17	204	23
Adolescent	65	10	105	14

[a] Based on vaccination strategies with ideal assumptions (100% coverage and 97% efficacy over 4 months of age and 0% efficacy for 0–4 months of age), applied to 1998 US birth cohort (3,776,389 persons) [19].

[b] Doses of vaccine administered calculated by multiplying 1998 birth cohort by number of vaccine doses in primary vaccination series.

infant strategy (two more than for the toddler strategy), the toddler strategy compared with the infant strategy would prevent 128 more cases and 15 more deaths per 10^6 doses of vaccine administered (Table 3B). Use of a C + Y formulation in an infant, toddler or adolescent strategy could reduce cases of meningococcal meningitis by 52, 49, or 27%, respectively, from the unvaccinated baseline (data not shown).

To determine how the cumulative analysis was affected by changes in vaccine coverage and efficacy, we performed a sensitivity analysis. We calculated the comparative impact on disease and deaths if the cumulative analysis were applied using the 'ideal' and 'current' age-specific assumptions for coverage and efficacy for a C + Y meningococcal conjugate vaccine used in each of the strategies. Compared with the assumption of using a C + Y vaccine with ideal coverage and efficacy, use of current coverage and efficacy assumptions would reduce the impact of infant and toddler strategies on disease incidence by 11 and 8%, respectively, and on deaths by 12% for both strategies. The adolescent strategy is more significantly affected by the current coverage and efficacy assumptions, with impact on disease reduced by 37% and on deaths by 33%. Qualitatively similar results were found when we examined the effect of systematic variations in coverage and efficacy on reducing disease and deaths after use of a C + Y meningococcal conjugate vaccine in each of the strategies (data not shown).

At a fixed point in time 10 years after initiating vaccination, the infant and toddler strategies would have greater impact on reducing annual cases of meningococcal disease than the adolescent strategy (28, 24 and 21%, respectively, with a C + Y vaccine) (Table 4), however, the adolescent strategy would have a greater impact on reducing meningococcal deaths. Use of a C + Y vaccine formulation in a combined infant, adolescent and college age strategy for 10 years could reduce meningococcal disease by 50%.

We also examined the impact of combining conjugate meningococcal serogroup components with the existing heptavalent pneumococcal conjugate vaccine [4]. This analysis indicates that such a combination vaccine could prevent 30% more deaths among persons 0–22 years of age than the heptavalent pneumococcal conjugate vaccine alone-far more deaths than could be prevented through addition of any other pneumococcal serotype (data not shown).

4. Discussion

Despite the best efforts of clinicians and public health practitioners, meningococcal disease continues to occur in US, killing some persons and leaving others permanently handicapped [1,18,33]. Our data suggest that routine use (in a strategy combining infant or toddler use with adolescents and college entry vaccination) of a serogroup C + Y meningococcal conjugate vaccine could prevent nearly 800 cases of meningococcal disease and 80 deaths in the US each year. Our analysis provides insight into the quantitative impact of targeting specific age-groups with meningococcal conjugate vaccines.

Rates of meningococcal disease are highest during infancy, and an infant vaccination strategy would eventually prevent disease and deaths over a wide age-range. However, if a meningococcal conjugate vaccine is first approved for toddlers or adolescents, rapid implementation of vaccination in these populations would also have a significant impact on disease. The toddler strategy would prevent more cases of disease and deaths per dose of vaccine, and because of the high case-fatality ratio for meningococcal disease among adolescents, the adolescent strategy would reduce deaths due to meningococcal disease disproportionately to its impact on disease prevention. Recent reports have found some college students to be at higher risk for meningococcal

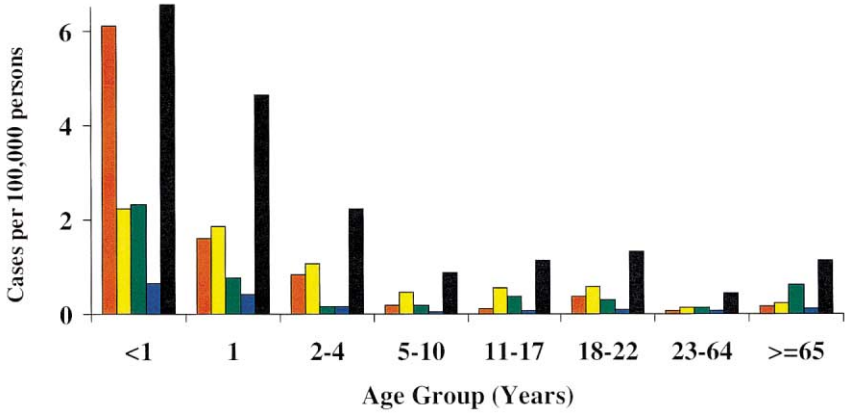

Fig. 1. Projected incidence of serogroup-specific meningococcal disease with serogroup B in red, serogroup C in yellow, serogroup Y in green, all other serogroups combined in blue and total meningococcal disease in black.

Table 4
Total meningococcal disease/deaths among persons 0–22 years of age and percent reduction from unvaccinated baseline after first 10 years of specific vaccination strategy[a]

Vaccination strategy	Serogroup C vaccine				Serogroup C+Y vaccine			
	Disease remaining	(%) reduction	Deaths remaining	(%) reduction	Disease remaining	(%) reduction	Deaths remaining	(%) reduction
No vaccination baseline	1621	–	130	–	1621	–	130	–
Infant	1301	20	100	23	1175	28	97	25
Toddler	1324	18	100	23	1239	24	98	25
Adolescent	1414	13	102	22	1284	21	84	35
College	1584	2	122	6	1565	3	122	6
Infant +adolescent +college	1079	33	68	48	814	50	47	64
Toddler +adolescent +college	1102	32	68	48	878	46	48	63

[a] Based on vaccination strategies with ideal assumptions (100% coverage and 97% efficacy for infants over 4 months of age and 0% efficacy for 0–4 months of age) applied to 1998 US census population [19].

disease [34,35], and new Advisory Committee on Immunization Practices (ACIP) recommendations [36] have prompted increased use of vaccine among college students, but use of meningococcal conjugate vaccine in this population would have minimal impact on overall rates of meningococcal disease and deaths.

Meningococcal polysaccharide vaccines are effective in preventing meningococcal disease in older children and adults [37,38], however, polysaccharide vaccines do not consistently reduce carriage. Our models suggest that adolescent vaccination would have a lesser impact on meningococcal disease rates than either infant or toddler strategies, but we did not include the impact that conjugate vaccine may have on lowering meningococcal carriage rates. If meningococcal conjugate vaccines act similar to Hib conjugate vaccines [31,39], reduction in carriage may decrease transmission to unvaccinated persons, resulting in herd immunity. Since meningococcal carriage rates are highest in adolescents and young adults [40,41], vaccination of adolescents with meningococcal conjugate vaccine could maximize herd immunity thus improving the effectiveness of this strategy.

Decisions about vaccine formulations are complicated by changes in the distribution of meningococcal serogroups. For example, consistent with earlier reports [42], we found that the proportion of meningococcal disease caused by serogroup Y has risen dramatically in US over the past decade. We determined that addition of a serogroup Y conjugate to a serogroup C conjugate vaccine used with an infant strategy could result in 48% greater reduction in meningococcal disease. If the same calculation were based on the serogroup distribution in 1990–1992, the projected disease reduction attributed to the addition of serogroup Y to a conjugate vaccine would have been 12% (data not shown). In contrast to this increase in serogroup Y disease, serogroup A has not been confirmed as a cause of meningococcal disease in US in nearly 20 years [18] despite its having been a major cause earlier in this century [43,44] and remaining very important internationally [45]. The recent outbreak of serogroup W-135 meningococcal disease among pilgrims returning from the Hajj raises the possibility that serogroup W-135, historically a minor cause of disease, could also rise to greater prominence in US and world-wide [46]. The reasons for these changes are not completely clear and, therefore, with our current level of understanding, future changes in serogroup distribution are difficult to predict distribution. Although our analysis indicates that the addition of serogroups W-135 and A components to a serogroup C+Y conjugate meningococcal vaccine would not have significant impact on current US rates of meningococcal disease (data not shown), uncertainties in the future importance of these serogroups make the a broader A/C/Y/W-135 conjugate vaccine formulation appealing for the greater flexibility it would provide in the face of future changes in US serogroup distribution [47]. Such a vaccine could also be used internationally despite variations in the global distribution of meningococcal serogroups [33].

Factors affecting implementation of vaccination programs can also affect the impact of specific strategies. For the infant and toddler strategies, use of current rather than ideal estimates of coverage and efficacy did not substantially change our conclusions. Since current adolescent vaccination rates are lower than infant or toddler rates, the utility of the adolescent strategy will

depend on improving vaccination coverage in this age-group. Due to of widespread public apprehension about meningococcal disease, higher adolescent coverage rates might be achieved for meningococcal conjugate vaccine than expected for other vaccines; this, in turn, could result in improved coverage rates for other adolescent vaccines. Implementation of a 3-dose infant meningococcal conjugate vaccine strategy is also complicated by the already crowded infant immunization schedule. A single-dose toddler vaccine could achieve greater impact per dose of vaccine with minimal changes to the existing vaccination schedule, but this would be at the cost of missing some preventable cases of meningococcal disease in infancy. Future combination vaccines that blend meningococcal conjugates with currently approved or soon-to-be-available vaccines may provide a way to protect infants with a simplified vaccine schedule [48]. Although these combination vaccines are still early in development, the addition of a meningococcal component would broaden the impact of existing vaccines on childhood diseases. Although a cost-effectiveness analysis for use of meningococcal conjugate vaccines in isolation or in combination with other vaccines was beyond the scope of our study, vaccines combining meningococcal conjugate components with other childhood vaccines would likely also provide a way for improving cost-effectiveness of meningococcal conjugate vaccination.

While the choice of an appropriate meningococcal conjugate vaccination strategy is clearly complex, our data demonstrate that over the next 10 years, several strategies and vaccine formulations could be employed to maximize public health impact and decrease the burden of meningococcal disease in US. Eventually, routine use of combination vaccines administered in the first 6 months of life which include pneumococcal, Hib and meningococcal conjugates, as well as an effective serogroup B meningococcal vaccine may offer the best hope for dramatically and efficiently reducing morbidity and mortality from bacterial meningitis.

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Appendix A

In addition to the authors listed, the ABCs team also includes: **California**: California Emerging Infections Program: Arthur Reingold, (also with University of California, Berkeley), Pam Daily, Gretchen Rothrock; California Department of Health Services, Berkeley: Duc Vugia, **Connecticut**: Connecticut Emerging Infections Program and Connecticut Department of Public Health, Hartford: Matt Cartter, Jim Hadler, Patricia Mshar, Nancy Barrett, Craig Morin; **Georgia**: Georgia Emerging Infections Program and Emory University, Atlanta: Monica Farley, David Stephens, Wendy Baughman; Georgia Department of Human Resources, Atlanta: Paul Blake, Katherine Combs, Jane Koehler; **Maryland**: Maryland Emerging Infections Program and Johns Hopkins University School of Hygiene and Public Health, Baltimore: Lee Harrison, Lillian Billmann, Peggy Pass; Department of Health and Mental Hygiene, Baltimore: Diane Dwyer; **Minnesota**: Minnesota Emerging Infections Program and Minnesota Department of Health, Minneapolis: Rich Danila, Jean Rainbow, Catherine Lexau; **New York**: New York Emerging Infections Program and New York State Department of Health, Albany: Dale Morse, Hwagan Chang, Perry Smith, Shelley Zansky; Monroe County Health Department, Rochester: Nancy Bennett, Barbara Damaske; **Oklahoma**: State Department of Health, Oklahoma City: Patricia Quinlisk, Laurie Smithee; **Tennessee**: Tennessee Emerging Infections Program and Vanderbilt Medical Center, Nashville: Brenda Barnes, Allen Craig, Louis Lefkowitz, William Schaffner; **CDC**: Division of Bacterial and Mycotic Diseases: Melissa Berkowitz, Katherine A. Robinson, Carolyn Wright, Cynthia Whitney, Chris A. Van Beneden, Tanja Popovic.

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